I. REMARKS

Claims 1-5, 7, 9-22 and 31-35 are cancelled herein. New Claims 36-41 have been added, leaving Claims 23-30 and 36-41 pending in the above-identified application. A Petition for Extension of Time along with the required payment accompanies this Amendment.

II. ARGUMENTS

A. Rejection Under 35 U.S.C § 112, 2nd Paragraph

Claims 23-30 are rejected under 35 USC § 112, 2nd paragraph as being incomplete for omitting an essential step which is the step of administering the pharmaceutical aerosol to the patient. New independent Claim 36 is added herein which clearly recites all of the steps in Applicants' claimed method. Since the remainder of the pending claims depend directly or indirectly from Claim 36 it is believed that Examiner's rejection of Claims 23-30 under Section 112, 2nd paragraph has been overcome.

B. Rejection Under 35 USC §102(b)

The claims are rejected under 35 U.S.C. §102(b) as being anticipated by Gonda et al., US Pat. 5,743,250 (the '250 patent). Examiner contends that:

> "Gonda teaches a method of delivering an aerosol suspension to the lungs...the suspension consists of insulin suspended in ethanol ...Gonda teaches that excipients can be added to the suspension".

Examiner's assessment of Gonda is accurate but it is the "30,000 feet" view of what the reference teaches and not the "particular" view that would be taken by one skilled in the art in considering the teachings of Gonda.

There are several significant differences between the method described and claimed by Gonda and Applicants' claimed method. All of these differences flow from two key features of the Gonda method. Firstly, the insulin aerosol that is produced during the practice of the Gonda method is produced using a device that is not an EHD means. Secondly, to achieve what

Gonda explicitly teaches as the critical feature of his invention, the patient is required to carry out an "inhale-exhale maneuver".

In a typical EHD device, a fluid delivery means delivers fluid to be aerosolized to a nozzle maintained at high electric potential. One type of nozzle used in EHD devices is a capillary tube that is capable of conducting electricity. An electric potential is placed on the capillary tube which charges the fluid contents such that, as the fluid emerges from the tip or end of the capillary tube, a so-called Taylor cone is formed. This cone shape results from a balance of the forces of electric charge on the fluid and the fluid's own surface tension. Desirably, the charge on the fluid overcomes the surface tension and at the tip of the Taylor cone, a thin jet of fluid forms and subsequently and rapidly separates a short distance beyond the tip into an aerosol. Studies have shown that this aerosol (often described as a soft cloud) has a uniform droplet size and a high velocity leaving the tip but that it quickly decelerates to a very low velocity a short distance beyond the tip.

A desirable feature of aerosolization using an EHD means is tight control of the particle size distribution of the resulting aerosol resulting in nearly monodisperse aerosols. In the case of delivery of a medicament aerosol to the deep lung (alveolar region) control of particle size is very important in order that most of the inhaled droplets reach the alveolar region. Also, EHD aerosolization is a gentle process that causes little or no damage to labile proteins and peptides during the aerosolization process.

The aerosolization means described by Gonda mechanically creates the aerosol of the insulin formulation by forcing the formulation through the pores of a membrane (structure 3 in Fig. 3 or Fig. 4). The diameter of the aerosol particles of the insulin formulation is generally about one to three times the diameter of the pores of the membrane. Accordingly, if the pore size was 2 microns the resulting aerosol particle diameter would be about 6 microns.

Gonda teaches that it is technically difficult to make pores of 2.0 microns or less (Col. 3, lines 63-67). In order to be effective the insulin must be delivered to the deep lung; consequently, the target particle size should be less than 5 microns. In order to control the particle size, the aerosolization device used by Gonda heats the air to evaporate all or most of the formulation liquid.

As would be appreciated by one skilled in this art, reliance on evaporation of the formulation liquid to control particle size adds additional complexity to the formation of the aerosol and thus, practice of the method. One has to account for ambient temperature and

humidity as this could affect the rate of evaporation. Gonda specifically teaches that these factors must be taken into consideration at Col 12, lines 33-67 and Col. 13, lines 1-25.

At the time Gonda filed on the invention described in the '250 patent it was known to administer aerosolized insulin formulations to humans and animals. (Col. 1, lines 55-67 and Col. 2, lines 1-61). The aerosols were either produced using a metered dose inhaler (MDI) or a nebulizer. Gonda teaches (Col. 18, lines 6-14) that the use of MDIs and nebulizers have a number of disadvantages which result in the inability to use these devices to repeatedly deliver the same amount of drug to the patient in large part due to the inability to control particle size.

Gonda clearly teaches one skilled in the art that the type of device used to produce the aerosol of the insulin formulation is an integral part of the practice of the methods described by Gonda. The practiced of the method claimed by Applicants requires the use of an EHD aerosolization means to produce the aerosol from the liquid carrier formulation. This is a significant difference between the practice of Applicants method and that disclosed by Gonda.

Gonda teaches (Col. 12, lines 4-10) that the critical feature of his invention is the enhanced rate at which insulin is brought into the circulatory system and the reproducibility of the release of a tightly controlled amount of drug at a particular point in the inspiratory cycle so as to assure the delivery of a controlled and repeatable amount of drug to the lungs of each individual patient and allow further insulin to be absorbed more quickly if needed. This critical feature is achieved by the patient performing an "inhale-exhale maneuver".

Gonda uses the term "inhale-exhale maneuver" to refer to the process of "inhaling maximally" followed by the process of "exhaling maximally". The term "inhaling maximally" means that the patient makes a maximum effort to inhale air into the lungs and the term "exhaling maximally" means that the patient makes a maximum effort to exhale all air from the lungs (Col. 8, lines 24-36).

The practice of the method of the invention claimed herein does not require "inhale-exhale maneuvers" to get enough information into a microprocessor in the aerosolization device to allow the device (as opposed to the patient) to make the decision as to when to release drug or to allow insulin to be absorbed more quickly into the circulatory system.

Gonda teaches (Col. 11, lines 40-47) that the Gonda aerosolization device is not directly actuated by the patient in the sense that no button is pushed nor valve released by the patient applying physical pressure. On the contrary, the device of the invention provides that aerosolized insulin formulation is released automatically upon receipt of a signal from a

microprocessor programmed to send a signal when data is received from a monitoring device such as an airflow rate monitoring device.

In the practice of the method of applicants' invention, the patient uses the EHD device (inhaler) much like she would use a conventional MDI. Unlike the device of Gonda which releases drug independent from the patient, in the practice of Applicants' method the patient controls the actuation of the aerosolization process and release of the aerosol from the EHD inhaler.

There are significant and meaningful differences between the method taught by Gonda and the method claimed by Applicants herein. Gonda describes the critical features of his method in great detail. Examiner may not substitute his opinion of the value or weight of such differences when Gonda teaches their importance.

In order to anticipate Applicants' claimed method, the Gonda reference must disclose each element of method claimed herein. W.L. Gore & Assocs. V. Garlock, Inc., 220 USPQ 303. The Gonda reference contains absolutely no disclosure of aerosolization of an insulin formulation using an EHD device. Further, Gonda specifically teaches the importance of the "inhale-exhale maneuver" which is the step in the methods disclosed by Gonda necessary to achieve the critical feature of the Gonda method. Finally, there is no suggestion provided by Gonda, which would lead one skilled in this art to ignore the voluminous (46 columns!) specific and detailed teachings of the '250 patent to arrive at the invention claimed herein.

C. 35 U.S.C. §103 Rejection

Based on the analysis and arguments presented in response to the Section 102(b) rejection Applicants submit that the rejection of the claims under Section 103(a) has been overcome.

D. Conclusion

Based on the amendments and arguments made herein, it is respectfully asserted that Claims 23-30and 36-41 directed to a method of administering a highly aqueous medicament aerosol to a patient using an EHD aerosolization means are in condition for allowance. Examiner is respectfully requested to withdraw the rejections under 35 USC §112 , 35 USC §102(b) and 35 USC §103(a) and to issue a Notice of Allowance.

Respectfully submitted,

Dated: November 10, 2003

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Inventors:	Cowan et al.
Title:	Stable, Aerosolizable Suspensions of Proteins in Ethanol

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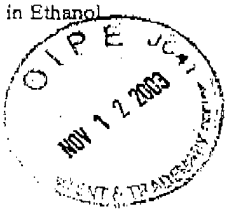

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